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(21) International Application Number: PCT/EP96/04860 (22) International Filing Date: 7 November 1996 (07.11.96) (30) Priority Data: MI95A002337 14 November 1995 (14.11.95) IT (71) Applicant (for all designated States except US): ISTITUTO GENTILI S.P.A. [IT/IT]; Via Mazzini, 112, I-56125 Pisa (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): BARELLI, Giulio [IT/IT]; Via Mazzini, 112, I-56125 Pisa (IT). DE REGIS, Massimo [IT/IT]; Via Mazzini, 112, I-56125 Pisa (IT). (74) Agent: MINOJA, Fabrizio; Studio Consulenza Brevettuale, Via Rossini, 8, I-20122 Milano (IT).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: A GLIBENCLAMIDE-METFORMIN COMBINATION FOR THE TREATMENT OF DIABETES MELLITUS OF TYPE II (57) Abstract A combination of glibenclamide and metformin such that, when administered in the form of pharmaceutical composition in the treatment of diabetes mellitus of type II, the ratio between the two active principles allows to obtain an optimum therapeutical effect at any time of the progression of the disease, avoiding to make use of the insulin therapy in the most severe cases.		

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A GLIBENCLAMIDE-METFORMIN COMBINATION FOR THE TREATMENT OF DIABETES MELLITUS OF TYPE II

The present invention relates to the use of a combination consisting of glibenclamide and metformin in one specific ratio as medicament for the treatment of diabetes mellitus of type II.

5 Non-insulin dependent diabetes of type II (NID) is known to be a frequent metabolic disease and the main cause of hyperglycemia. In recent years, diabetes mellitus of type II has been proved to be a heterogeneous disease, with complex, unclarified
10 metabolic aspects, which disease is characterized by three main metabolic abnormalities contributing to hyperglycemia: the partial or complete decrease in insulin secretion, the resistance of the peripheral tissues to insulin and the increased hepatic production
15 of glucose in fasting conditions.

Diet and physical exertion are unanimously recognized to be the foundation of the therapy of diabetes of type II: both of them lead to a reduction in insulin-resistance and, in the long run, to an
20 improvement in the pancreas secretive deficit.

However, these provisions are insufficient and a pharmacological aid with oral hypoglycemic agents is necessary. At present, the two main families of oral hypoglycemic agents available are sulfonylureas and
25 biguanides.

The use of sulfonylureas and biguanides in monotherapy, in most cases, allows to obtain an effective glycometabolic control for some years, if an

appropriate diet and behavioural regimen are kept. Nevertheless, the efficacy of the therapy with oral hypoglycemic agents can decrease with time.

After a positive starting response which can last
5 4-5 years, monotherapy becomes ineffective in a considerable percentage of patients. These are the so-called "secondary failures" of the therapy with oral hypoglycemic agents. Such a failure is estimated to occur each year in 5-10% of the patients under therapy
10 with sulfonylureas, therefore after 10 years, only 50% of the patients still show a satisfactory response.

The secondary failure in patients under treatment with metformin appears to have an incidence superimposable to the above mentioned one.

15 Recent studies show that besides a qualitative/quantitative deficiency of insulin secretion, the combined occurrence of insulin-resistance conditions is at the bottom of NID diabetes.

Since sulfonylureas are capable of stimulating
20 insulin release, but are not capable of acting on insulin resistance, and biguanides are able to act on insulin resistance, whereas they are not able to stimulate insulin secretion, the therapeutical rationale of said studies suggested the use of combined
25 formulations of medicaments capable of finding a remedy for both the deficiency in insulin secretion and the insulin-resistance condition.

Vigneri et al. (Diabete & Metabolisme, 1991, (17), 232-234), faced the problem of secondary failure to
30 sulfonylurea therapy in NID diabetes. The authors proposed a combination of glibenclamide-metformin in a

daily dosage of 15 mg and 1500 mg, respectively, in alternative to insulin therapy in addition to glibenclamide.

5 The combined therapy (sulfonylurea + biguanide) plays therefore a specifically important therapeutical role, since it allows to obtain an effective metabolic control in those patients with diabetes of type II, in which the therapy with only sulfonylureas or only biguanides becomes ineffective with time.

10 Two biguanides are used in the oral therapy of diabetes of type II: phenformin and metformin. Although the former is still widely used, a number of data in literature clearly show that metformin exerts an effective normoglycemic action with no risk of lactic
15 acidosis in the patients, as it can occur in some cases when using phenformin. Therefore, it is generally accepted that metformin is the preferred biguanide in the therapy of diabetes of type II.

The Applicant found, during clinical experiments,
20 that the sulfonylurea maximum daily dose considered optimum for the most severe, barely controllable cases is 15 mg. However, such a dose has to be combined with a biguanide maximum daily dose of 1500 mg in order to obtain the maximum therapeutical effect together with
25 the reduction of untoward effects.

At present 4 combinations are marketed which use a combination of metformin with glibenclamide (Table 1). In the first combination, glibenclamide dose is 2.5 mg and metformin (expressed as the hydrochloride) dose is
30 500 mg for each tablet, namely a weight ratio of 1:200. In the other combinations, doses are respectively: 2.5

mg of glibenclamide and 400 mg of metformin, namely a weight ratio of 1:160.

TABLE I

Ready-to-use preparations of sulfonylurea (S) -
Metformin (M) available at present:

Name	Manufacturer	S (dose/cp)	M (dose/cp)

10	Glucomide	Lipha	Glibenclamide
			Metformin
		(2.5 mg)	(500 mg)
	Glibomet	Guidotti	Glibenclamide
			Metformin
		(2.5 mg)	(400 mg)
	Suguan M	Hoechst	Glibenclamide
			Metformin
		(2.5 mg)	(400 mg)
15	Bi-Euglucon M	Boehringer M	Glibenclamide
			Metformin
		(2.5 mg)	(400 mg)

It should be noted, however, that none of these formulations attain the optimum therapeutical effect due to the quantitative unbalance of the medicaments in combination. In fact, using the above mentioned formulations, in order to obtain the sulfonylurea maximum dose of 15 mg, which we consider optimum for the most severe, barely controllable cases, 6 tablets of the medicament should be taken, thus receiving 2400-3000 mg of metformin, which is a dose markedly higher than the maximum one we recommend (1500 mg).

Therefore, the still unsolved problem is to find a combination capable of obtaining the maximum increase in the therapeutical effect with balanced doses of the single medicaments, thereby decreasing in parallel their

untoward effects.

Such a research is of paramount importance, taking into account that in diabetes of type II it is often necessary to progressively increase with time the
5 hypoglycemic medicament doses.

The present invention solves the problem to provide medicament effective for the treatment of diabetes mellitus of type II in cases of secondary failure to a combination of glibenclamide-metformin currently used in
10 therapy.

Abstract of the invention

Now it has been found that a combination of glibenclamide and metformin (expressed as the hydrochloride) in a 1:100 weight ratio, so as to allow a
15 daily administration of 15 mg of glibenclamide and 1500 mg of metformin, is suitable to the preparation of a medicament useful for the treatment of diabetes mellitus of type II at any time of the progression of the disease, from its onset to the most severe cases.

20 Therefore, it is an object of the present invention the use of the above mentioned combination in admixture with conventional carriers and excipients for the preparation of a medicament for the treatment of diabetes mellitus of type II, particularly in the cases
25 of "secondary failure" to a combination of glibenclamide-metformin currently used in therapy.

Detailed disclosure of the invention

According to a first preferred embodiment of the present invention, the combination of the two active
30 ingredients is used in a medicament in the form of tablets with a dosage of 5 mg of glibenclamide and 500

mg of metformin. This medicament is useful for the treatment of diabetes mellitus of type II.

The balance of said doses makes the therapeutical effect optimum at any time of the progression of the disease, starting from minor cases to the most severe ones, and particularly, when it is necessary to increase progressively with time the doses of the two substances.

On the contrary, when combination ratios different from those of the present invention are used, the following cases are likely to occur:

- when the ratios are lower than the recommended ones, the number of metabolically controlled diabetic patients will definitely be lower;
- when the recommended doses are exceeded, there will be an actual risk of untoward effects.

Therefore, the target area of the patients responding to the therapy will increase and at the same time the onset of therapeutical risks will be highly decreased only when the two medicaments are administered in combination at the doses present in the tablet, or at multiple and submultiple doses of the same.

Moreover, it has been proved that a dose increase beyond the maximum limits herein recommended of 15 mg of glibenclamide and 1500 mg of metformin daily causes no further favourable therapeutical effects.

Finally, it should be stressed that the above mentioned doses can theoretically be attained also using the two medicaments separately. However, this involves the need of taking twice as many tablets a day, with clear compliance problems, especially in the elderly patients which require concomitant therapies for other

pathologies which are frequently connected with diabetes, such as hypertension and vascular diseases.

Said combination of dosages can be used starting from the onset of the disease in NID diabetics since the
5 ratio of 5 mg of glibenclamide + 500 mg of metformin will always be balanced, in both the multiple and submultiple dosages. In fact, when the tablets are subdivided, thus obtaining minor and/or fractional daily dosages, the fixed ratio, which is the balanced one, is
10 always maintained. Therefore, according to a second embodiment of the present invention, the medicament is in the form of a divisible tablet containing the combination described above.

Alternatively, tablets containing fractions of the
15 preferred dosage can be prepared, always keeping the 1:100 ratio between the two active principles.

Analogously, in the most severe cases of diabetes with metabolic decompensation, which cannot be controlled with the commercially available combination
20 medicaments, (so that the patients should turn to insulin therapy), the combination of the invention allows to treat them, still and for a long time, with the oral therapy, with obvious benefits for the patients themselves.

25 In confirmation of what stated above, the study profile and the results of the experimentation carried out are reported in the following.

Study profile

Sample size

30 About 100 diabetics of type II (non insulin-dependent) have been studied. The sample was calculated

so that a clinically significant average reduction of the values of glycated hemoglobin A1c equal to or higher than 0.6% and an average reduction of glycemia equal to or higher than 18 mg/dl in the 16 weeks of treatment could be detected. The standard deviations envisaged for HbA1c and for fasting glycemia are 1.46% and 44 mg/dl. The analysis makes use of a significance level of 0.05 and a test power of 0.80 (two-tail test).

Description of the studied panel

98 Patients with diabetes mellitus of type II (non insulin-dependent) were studied. The average age of the subjects was 57.3 ± 6.6 years.

The panel consisted of 45 males (46%) and 53 females (54%) of superimposable age.

Starting metabolic profile

The fasting glycemia measured at examination 1 was 219 ± 37 mg/dl (95% confidence limits: 211-226 mg/dl; 10-90th percentile: 184-272 mg/dl), 24 hour glycosuria 25 ± 36 g (95% confidence limits: 18-33 g; 10-90 percentile 7-64 g), no acetonuria in all of the patients, glycated hemoglobin A1c $9.1 \pm 0.9\%$ (95% confidence limits 8.9-9.2%; 10-90th percentile: 8-10.1%).

TABLE A

Metabolic profile of the subjects studied in each centre.

5	Centre	1	2	3	4	ANOVA Oneway p=
	N	9	31	38	20	
	Fasting					
10	glycemia (mg/dl)	219±41	211±33	221±42	226±29	ns
	24 hour					
	glycosuria (g/24 hours)	11±14*	25±15	37±54	* *	0.026
15	Acetonuria	0	0	0	0	--
	Glycated					
	hemoglobin A1c (%)	8.8±1,1	9.1±0.7	8.8±1,0	9.6±0.4*	0.002

20 * p < 0.05 Centre 1 vs Centre 3

** At the Centre 4, glycosuria was doses with a semiquantitative procedure

* p < 0.05 Centre 4 vs Centres 1, 2. 3

Evaluation of the efficacy of the treatment

25 The parameters the evaluation of the efficacy of the treatment is based on are:

1. fasting glycemia;
2. post-prandial glycemia;
3. 24 hour glycosuria;
- 30 4. presence of acetone in the urines;
5. glycated hemoglobin (HbA1c).

10

Other important parameters evaluated during the study are:

1. body weight
2. total cholesterol plasma levels;
- 5 3. HDL cholesterol plasma levels;
4. LDL cholesterol plasma levels;
5. arterial pressure values.

Fasting glycemia

The average values of the fasting glycemia
10 evidenced during the study are reported in Table B.

* $p < 0.001$ vs Examination 1 and Examination 2

§ $p < 0.001$ vs Examination 1. $p < 0.01$ vs Examination 2

$p < 0.05$ vs Examination 1

5 \$ $p < 0.01$ vs Examination 2

In the whole panel, the fasting glycemia underwent a significant reduction already after two weeks of treatment ($p < 0.001$); said reduction was maintained subsequently during all the study (16 weeks). Similar results were obtained from the analysis carried out at the single Centres (Centres 2-4). Only in Centre 1, no reduction in glycemia was detected, partly probably due to the small number (n. 9) of the studied subjects (Table B).

15 Table C reports the results of the glycemia course in subjects stratified as a function of the Body Mass Index (BMI; normal weight: BMI < 25 kg/m². n = 21; overweight BMI 25-30 kg/m². n = 52; obese BMI ≥ 30 kg/m². n = 259).

TABLE C

Fasting glycemia: changes during the study.

The subjects were stratified depending on BMI (Body Mass Index).

Examinations	1	2	2b	3	4	5	6	Variance
Weeks	-3	0	2	4	8	12	16	for analysis repeated
								measurements p <
<hr/>								
BMI	1 Factor analysis							
< 25 kg/m ²	214	212	180*	167*	173*	175*	168*	0.0001
25-30 kg/m ²	220	223	192*	196*	194*	186*	182*	0.0001
≥ 30 kg/m ²	227	247	208§	208§	207§	196§	205§	0.035
Anova	ns	ns	ns	0.02	ns	ns	ns	
Oneway (p <)	2 Factor analysis							
among groups	0.0001							
among examinations	0.0001							

* $p < 0.001$ vs Examination 1 and Examination 2

§ $p < 0.05$ vs Examination 2

The effects of the treatment are clear (variance analysis for repeated measurements, $p < 0.0001$) in the subjects with normal body weight and in the overweight subjects (BMI 25-30 kg/m²), which are less sensitive, but still statistically significant ($p < 0.035$ in the obese subgroup (BMI > 30 kg/m²)).

Post-prandial glycemia

The mean values of the fasting glycemia evidenced during the study are reported in Table D. The post-prandial glycemia, measured at the beginning and at the end of the study, underwent a significant reduction both in the whole panel (318 to 267/mg/dl) and in each of the subgroups defined depending on the Body Mass Index.

TABLE D

Post-prandial glycemia: changes during the study.

In the second part of the table the subjects were stratified depending on the BMI (Body Mass Index).

5	-----			
	Examinations	2	6	Student's t test for coupled data weeks (p <)
		0	16	

10	Whole	318	267	0.0001
	Panel:	(64)	(79)	

	BMI:			Variance analysis for measurements (1 factor)
15	<25 kg/m ²	317	252	0.0001
	25-30 kg/m ²	320	263	0.0001
	≥30 kg/m ²	313	287	0.001
	Anova	ns	ns	
	Oneway (p <)			
20				2 Factor analysis
	among groups			ns
	among examinations			0.0001

Adverse events

25 The untoward effects were infrequent and slight; in practice, only gastro-intestinal untoward effects such as nausea, abdomen pains and diarrhoea, more or less combined together, occurred.

Conclusions about the therapeutical efficacy

30 In the clinical study carried out, the proposed combination (glibenclamide 5 mg - metformin 500 mg) was

16

administered for 16 weeks to patients with diabetes of type II, in which the combined treatment with glibenclamide-metformin at the presently available dosages gave no longer an acceptable metabolic control.

5 The main result from the evaluation of the efficacy consists in the significant decrease in the fasting glycemia (-35 mg/dl), in the glycemia 2 hours after meals (-51 mg/dl) and in the HbA1c (-0.9%).

 These results are of particular value when
10 considering that:

1. Whereas the patients with a more severe diabetic condition (so as to be necessary the use of high dosages of glibenclamide and metformin), actually
15 were no longer responsive to the sulfonylurea-metformin combinations commercially available and as a consequence it was necessary to start the subsequent therapeutical option, i.e. the addition of insulin to the oral therapy or the complete substitution of the latter with insulin itself.

20 These cases were treated successfully and the obtained results prove that the combination glibenclamide 5 mg + metformin 500 mg is an important therapeutical tool, which allows to obtain an effective control of glycid metabolism
25 still making use of the only hypoglycemizing oral therapy, thus obtaining a further favourable effect on life-quality of the patients themselves.

2. On the contrary, for the less severe cases, the ratio 5 mg of glibenclamide + 500 mg of metformin,
30 can be subdivided as desired, thereby having lower and/or fractional daily dosages thus allowing to

treat the disease from its onset, as the glibenclamide to metformin ratio, even when fractioned, will turn out to be very well balanced.

As far as the industrial applicability aspects are
5 concerned, the medicaments according to the invention are provided in the form of pharmaceutical composition, which can be prepared according to conventional techniques known to those skilled in the art, for example as described in Remington's Pharmaceutical
10 Sciences Handbook, Mack. Pub., N.Y., U.S.A.

Among the pharmaceutical compositions intended for the treatment of diabetes mellitus of type II, those which are administered orally are preferred, such as coated or non-coated tablets, capsules, sugar-coated
15 pills, granulates, oral suspensions, microgranules, controlled-release tablets.

Metformin is used preferably in the form of metformin hydrochloride salt. Of course, it is also possible to use equivalent amounts of other phosphate,
20 solfite, dithionate, acetate, benzoate, citrate salts and the like, optionally together with suitable buffers.

On the contrary, glibenclamide is an insoluble substance.

Since said compound has to be administered in
25 comparatively high dosages (5 mg of Glibenclamide + 500 mg of Metformin HCl) and for long times in order to obtain a complete action, the oral route was considered the simplest administration method.

In the galenic study carried out to accomplish the
30 most suitable pharmaceutical form, the following objectives were taken into account:

- ready contact of the active ingredient in the dispersed state with gastroenteral mucosae
- easiness of swallowing
- posology flexibility
- 5 - optimization of the technological characteristics of the granulate for the working up with fast devices
- choice of the material suitable for the preservation of the product
- 10 - manufacturing process easy to carry out and economical.

Considering the high unitary dosage required, the pharmaceutical formulation in lozenge-shaped tablets, with a central breaking division, has been chosen since
15 it is considered the most suitable one. Such a tablet can have the composition as shown in Example 1.

In fact this allows, with comparatively limited sizes, to carry suitably the active ingredient, so as to combine a favourable working-up with optimum bio-
20 pharmaceutical and technical characteristics besides an improved swallowability.

The tablets were subjected to wet-granulation; the excipients reported hereinbelow were selected, after a number of laboratory tests in order to find the amount
25 of each excipient to attain the best workability together with biopharmaceutical and technological characteristics of the tablets:

- maize starch: diluent and disintegrant;
- precipitated silica: it promotes the cohesion of
30 the granulates improving their flowability;
- microcrystalline cellulose (Avicel PH 101): a

diluent, which favours the formation of compact granules and therefore of more resistant tablets contributing at the same time to disaggregation of the pharmaceutical form, promoting the penetration of liquid inside it by capillarity;

- gelatin: a binder used in solution to wet the granular mixture;
- glycerin: it is used in the gelatin solution to promote wetting and as a plasticizer;
- 10 - talc: a lubricant;
- magnesium stearate: a solid lubricant which is effective in amounts which do not significantly affect the disaggregation time of the tablets.

In order to improve handling and swallowing, a coating was moreover applied onto the tablets, which consists of a methylhydroxypropyl cellulose film as a film-forming agent, titanium dioxide as an opacifier and polyethylene glycol 400 as a plasticizer. The compatibility among the active ingredient and the selected excipients was ascertained by preliminary accelerated stability studies.

Finally, for the choice of the container, the physico-chemical characteristics of the active ingredient and of the tablet were considered in order to guarantee a safe preservation; the medicament of the invention showed a very good stability in an opaque blister consisting of PVC/PVDC and aluminium.

The manufacturing process was carried out by wet granulation both by means of kneading in a fast granulator and drying in air-circulation drier, and in fluidized bed granulator-drier. In both cases, tablets

with the desired characteristics were obtained.

The following examples further illustrate the invention.

EXAMPLE 1

5 **A coated tablet contains:**

	Glibenclamide	mg	5.00
	Metformin hydrochloride	mg	500.00
	Maize starch	mg	57.50
	Precipitate silica	mg	20.00
10	Microcrystalline cellulose	mg	65.00
	Gelatin	mg	40.00
	Glycerin	mg	17.50
	Talc	mg	17.50
	Magnesium stearate	mg	7.50
15	Methylhydroxypropylcellulose	mg	12.50
	Titanium dioxide	mg	6.25
	Polyethylene glycol 400	mg	1.25
	Unitary theor. average weight	mg	750.0

EXAMPLE 2

20 **Granulate sachets:**

	Glibenclamide:	mg	5.00
	Metformin hydrochloride	mg	500.00
	Polyvinylpyrrolidone	mg	22.00
	Saccharose	mg	1000.00
25	Mannitol	mg	821.00
	Sodium saccharinate	mg	10.00
	Orange flavour	mg	37.00
	Lemon flavour	mg	10.00
	Unitary theor. average weight	mg	2405.00

EXAMPLE 3**Suspension:**

	Glibenclamide	g	10.100
	Metformin hydrochloride	g	0.047
5	Sodium carboxymethylcellulose	g	0.079
	Microcrystalline cellulose	g	0.300
	Wild black cherry essence	g	0.089
	Anise essence	g	0.050
	Glycerol	g	10.000
10	Methyl p-hydroxybenzoate	g	0.050
	Saccharose	g	77.470
	Depurated water q.s. to	ml	100

CLAIMS

1. The use of a combination of glibenclamide-metformin hydrochloride in a 1:100 weight ratio for the
5 preparation of a single-dose medicament useful for the treatment of diabetes mellitus of type II in cases of secondary failure to a combination of glibenclamide-metformin hydrochloride in a weight ratio higher than 1:100.
- 10 2. The use of a combination of glibenclamide-metformin hydrochloride in a 1:100 weight ratio for the preparation of a single-dose medicament useful for the treatment of diabetes mellitus of type II in cases of secondary failure to a combination of glibenclamide-
15 metformin hydrochloride in a weight ratio of 1:160 or 1:200.
3. The use according to claim 1 or claim 2, characterized in that the medicament is suitable to the administration of a daily dosage of up to 15 mg of
20 glibenclamide and 1500 mg of metformin.
4. The use according to claim 1 or 2, characterized in that, in the medicament, the unitary dose contains 5 mg of glibenclamide and 500 mg of metformin.
5. The use according to claim 4, wherein the
25 medicament is in the form of a tablet.
6. The use according to claim 5, wherein the medicament is in the form of divisible tablet.
7. The use according to claims 1 or 2 and anyone of claims 3-7, characterized in that in the medicament
30 metformin hydrochloride is replaced with an equivalent amount of another pharmaceutically acceptable salt.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/04860

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/64 //(A61K31/64,31:155)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BIOSCI REP, 9 (3). 1989. 347-350., XP000570541 AL-AHMED F A A ET AL: "INTERACTION BETWEEN DIAZEPAM AND ORAL ANTIDIABETIC AGENTS ON SERUM GLUCOSE INSULIN AND CHROMIUM LEVELS IN RATS" see abstract	1-9
X	DIABETE METABOL., 1991, 17/1 BIS (232-234), FRANCE, XP000570538 VIGNERI R. ET AL: "Treatment of NIDDM patients with secondary failure to glyburide: comparison of the addition of either metformin or bed-time NPH insulin to glyburide" cited in the application see page 233, column 1, paragraph 3	1-9

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

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